REMARKS

The final Office Action dated December 23, 2010, has been received and carefully noted. The following remarks are being submitted as a full and complete response thereto.

Claims 1-11, 13-26 and 28-31 are pending in this application, with claims 1, 23, and 29-31 being independent. By this Amendment, claims 1, 8, and 29-31 have been amended, and claim 12 has been cancelled without prejudice to or disclaimer of the subject matter contained therein. Applicants submit that no new matter has been presented herein.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Rejections under 35 U.S.C. § 103(a)

Claims 1-11, 13-16, and 18-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins (U.S. Patent No. 6,031,004) and Balkan (U.S. Patent Publication No. 2003/0139434) as evidenced by Tyler (W.S. Tyler Canada, product and price catalog), Martin (U.S. Patent No. 6,110,497) and Shimizu (U.S. Patent No. 6,328,994). Applicants respectfully traverse this rejection.

The presently-claimed invention beneficially solves the problems associated with preparing oral dosage forms containing metformin by providing dispersible or orodispersible solid dosage forms comprising particles having a size that is lower than 710 microns upon dispersion in water. According to certain embodiments of the invention, when the particles that make up the oral dosage forms are dispersed in

water, the dispersion is homogenous, and no particle resulting from the disintegration of the dosage form has a size larger than 710 microns, as determined by passing the dispersion through a sieve having a nominal mesh size of 710 microns. *See* page 5. The particles that result from the disintegration of the dosage form include an internal core comprising the active ingredient and appropriate excipients, and an external layer comprising a sweetening agent and appropriate excipients. *See* page 11. As demonstrated by the data contained in Tables 11 and 12 of the specification, the presently-claimed dosage forms beneficially provide a pharmacokinetic profile that is equivalent to Glucophage®-brand metformin tablets, without any of the drawbacks of conventional formulations.

Timmins is cited for allegedly disclosing salts of the anti-diabetic agent metformin, including metformin fumarate and metformin succinate, which may be employed alone or in combination with another anti-hyperglycemic agent (*see* Abstract). Timmins discloses that the dosage form may be a tablet or capsule, among others (*see* column 4, lines 49-52). Timmins further discloses that the dosage forms may include from about 1% to about 80% excipients, such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, calcium carbonate, and microcrystalline cellulose (*see* column 5, lines 8-12); one or more binders such as polyvinylpyrrolidone (having a molecular weight of preferably about 40,000), lactose, starches and polyethylene, among others (*see* column 5, lines 15-23); about 2% to about 8% by weight of disintegrants, such as croscarmellose sodium, crospovidone/cross-linked polyvinyl pyrrolidone, sodium starch glycolate, corn starch and microcrystalline cellulose (*see* column 5, lines 24-30); other excipients such as preservatives, silicon dioxide, and

polymeric celluloses (*see* column 5, lines 34-46); and the sweetening agent xylitol, and the flavoring agents grape flavor, spice flavor and raspberry flavor (*see* column 10, lines 1-35).

In Example 4, Timmins discloses a tablet formulation containing the active agent metformin succinate in an amount of 80% (600/748x100), the binder hydroxypropylmethyl cellulose in an amount of 2% (15/748x100), the disintegrant croscarmellose sodium in an amount of 6% (45/748x100), the filler/diluting agent microcrystalline cellulose in an amount of 10% (80/748x100), and the additional excipient magnesium stearate. Timmins further discloses that the formulation of Example 4 is prepared by wet granulation, and includes the steps of mixing, granulating, drying and compressing into tablets (*see* column 7, lines 45-60).

Timmins also discloses that additional active ingredients may be included, such as pioglitazone (*see* column 3, line 64), thiazolidinedione/glitazone (*see* column 4, line 2), glimepride, glipyride, glipizide, chlorpropamide, glicazide and acarbose (*see* column 4, lines 24-26).

Regarding the size of the granules, the Office Action indicates that Timmins discloses that the mixtures of ingredients are passed through a #12 to #40 mesh screen (6:3), which according to Tyler indicates a size of from 425 microns to 1.7 mm (*see* Tyler, page 3, table columns 1-2). However, this statement is inaccurate.

The Office Action admits that Timmins does not disclose compositions that include a dipeptidyl peptidase inhibitor and/or a sugar coating. However, Balkan is cited for allegedly disclosing these features. Applicants submit that Timmins and Balkan also

fail to disclose or suggest dispersible or orodispersible solid dosage forms, as set forth in the pending claims.

Balkan is cited for disclosing combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound (*see* Abstract). Balkan further discloses compositions containing the anti-diabetic compound metformin, among others (*see* [0150]). Balkan further discloses the combination comprising DPP728 plus metformin (*see* [0175]). Balkan further discloses pharmaceutical preparations that are prepared by conventional mixing, granulating, and sugar-coating (*see* [0190]). Balkan further discloses that, if desired, the mixture may be processed to form granules, tablets, or sugar-coated tablet cores (*see* [0190]).

Shimizu is cited for allegedly disclosing orally disintegrating tablets comprising a coating layer and a core, where the core is 75-85% of the tablet weight (*see* col. 15, lines 20-40). Martin is cited for allegedly disclosing a dispersible tablet formulation composed of granulate particles and extragranular excipients, where the granulate particles may comprise 70-95% of the total tablet weight (*see* col. 2, lines 35-38).

The Office Action takes the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine a DPP-IV inhibitor with a metformin pharmaceutical composition, as suggested by Balkan, because Timmins suggests the use of metformin in combination with other anti-diabetic drugs, and because Balkan discloses that DPP-IV inhibitors are anti-diabetic drugs suitable for use with metformin. The Office Action asserts that one of ordinary skill in the art would have been motivated to combine Balkan with Timmins because the resulting formulation would have increased efficacy due to the combination of the two

anti-diabetic drugs. The Office Action also asserts that it would also have been obvious to produce a sweetener-coated formulation because the sweetener would have a more appealing taste for the user, and would therefore increase patient compliance. The Office Action further asserts that one skilled in the art would have had a reasonable expectation of success in producing the presently-claimed invention.

Applicants respectfully disagree with the positions taken in the Office Action.

Applicants submit that Timmins relates to dosage forms containing dibasic acid salts of metformin as an alternative to metformin hydrochloride, which is said to have an unpleasant taste and is considered problematic from a manufacturing standpoint. The alternative salts have improved taste and handling properties, and are "significantly less soluble in water than the hydrochloride salt and thus provide the opportunity for formulating metformin in controlled release systems." *See* col. 2, lines 38-43. Timmins fails to disclose or suggest the preparation of dispersible or orodispersible dosage forms, as claimed and as defined at page 4 of the present specification. Timmins provides no disclosure to enable one skilled in the art to prepare such a dosage form.

Timmins discloses at column 6, lines 2-3, that the medicament(s) and optional fillers are mixed and passed through a #12 to #40 mesh screen (425 microns to 1.7 mm), followed by adding optional filler/binder, a disintegrant, and a lubricant, and then mixing and compressing the mixture. The Office Action again takes the position that this disclosure renders the size feature of the presently-claimed invention obvious, but Applicants respectfully disagree. Applicants submit that although the active ingredient is sieved in Timmins, the steps of adding additional excipients to the sieved active

ingredient, followed by mixing and compressing, will result in a mixture containing particles that are larger than 710 microns.

Applicants submit the presently-claimed invention specifically relates to dispersible and orodispersible pharmaceutical compositions comprising particles containing a metformin active ingredient, and having a size that is less than 710 microns upon dispersion in water, where the particles comprise the various components set forth in the claims. Further, according to some embodiments, the metformin used in the presently-claimed invention preferably has a grain size of less than 100 microns, which is far smaller than the grain size for the active ingredients disclosed in Timmins. *See* page 8 of the present specification.

Balkan fails to remedy these deficiencies of Timmins with respect to the presently-claimed invention, because although it discloses combinations of DDP-IV inhibitors and an antidiabetic compound such as metformin, it utterly fails to disclose or suggest dispersible or orodispersible pharmaceutical compositions, or dosage forms that include particles having a size that is less than 710 microns upon dispersion in water.

Shimizu relates to an orally disintegratable tablet containing granules of the active agent lansoprazole, where the granules are less than 400 μm in size, including a coating of an enteric coating agent and a sustained-release agent. Martin relates to a tablet formulation for a beta-lactam antibiotic optionally combined with a beta-lactamase inhibitor, where the tablet is made by compacting a granulate that is from 100 μm to 2 mm in diameter. Shimizu and Martin are merely cited for disclosing the amount of the core relative to the tablet weight, and do not remedy the deficiencies of Timmins and

Balkan. Further, Applicants submit that one skilled in the art attempting to prepare a dispersible or orodispersible formulation containing metformin would not look to the disclosures of Shimizu and Martin. Shimizu and Martin relate to disintegratable dosage forms of active agents that are unrelated to metformin, and do not address the unique problems encountered when preparing formulations containing metformin.

Applicants also present the following comments regarding the "Response to Arguments" section.

The Office Action took the position that Applicants' particles will dissolve in water and therefore will pass through a sieve, and that only non-water soluble particles or poorly-water soluble particles, granules, or aggregates will remain to pass through mesh openings. However, this interpretation is not correct.

The claims are clear that the dispersible or orodispersible solid pharmaceutical compositions comprise ***particles*** that have a size lower than 710 µm upon ***dispersion*** into water. The claims state that the particles comprise a metformin active ingredient, a binding agent, a disintegrating agent, a diluting agent, a sweetening agent, and one or more additional excipients. These particles are present in a dispersion in the claims, and are not merely "dissolved" as stated in the Office Action. This interpretation of the claims ignores the differences between a dispersion and a solution. One skilled in the art would understand that dispersed particles containing multiple ingredients (as set forth in the claims) are distinct from a solution of dissolved dosage form components (the interpretation of Timmins relied upon in the Office Action). For at least these reasons, Applicants' claims specifically and unambiguously exclude the interpretation of Timmins used in the Office Action to maintain the rejections.

Accordingly, because the combination of Timmins and Balkan fails to disclose or suggest all of the features of the presently-claimed invention, and the deficiencies are not remedied by further combination with Tyler, Shimizu, and Martin, no *prima facie* case of obviousness has been established.

In view of the amendments and remarks presented above, Applicants submit that claims 1-11, 13-16, and 18-28 are not unpatentable over any combination of Timmins, Balkan, Tyler, Shimizu, and Martin, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 12 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Timmins and Balkan, as evidenced by Tyler, as applied to claims 1-11, 13-16, and 18-28 above, and further in view of Bonhomme (U.S. Patent No. 6,372,790).

Without conceding the propriety of this rejection, Applicants submit that it is moot in view of the cancellation of claim 12.

Claim 29 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Timmins and Balkan, as evidenced by Tyler, as applied to claims 1-11, 13-16, and 18-28 above, and further in view of Ohno (U.S. Patent No. 4,017,598), and further evidenced by Bennett ("Pharmaceutical Production: An engineering guide," 2003, Institution of Chemical Engineers, Chapter 6, pp. 111-153). Applicants respectfully traverse this rejection.

The deficiencies of the combination of Timmins, Balkan, and Tyler are discussed above.

Ohno is cited for allegedly disclosing adding a sweetener as an extragranular excipient before the final step of tablet compression.

Bennett is cited for allegedly disclosing the knowledge of a person having ordinary skill in the art of pharmaceutical formulation at the time the presently-claimed invention was made.

Applicants submit that Ohno and Bennett fail to remedy the deficiencies of the combination of Timmins, Balkan, and Tyler.

In view of the amendments and remarks presented above, Applicants submit that claim 29 is not unpatentable over any combination of Timmins, Balkan, Tyler, Ohno, and Bennett, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 30 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Timmins and Balkan as evidenced by Tyler as applied to claims 1-11, 13-16, and 18-28 above, and further in view of Venkatesh (U.S. Patent No. 6,475,510), and further evidenced by Bennett. Applicants respectfully traverse this rejection.

The deficiencies of the combination of Timmins, Balkan, and Tyler are discussed above.

Venkatesh is cited for allegedly disclosing dry granulation, as well as adding a sweetener as an extragranular excipient before the final step of tablet compression.

Bennett is cited for allegedly disclosing the knowledge of a person having ordinary skill in the art of pharmaceutical formulation at the time the presently-claimed invention was made.

Applicants submit that Venkatesh and Bennett fail to remedy the deficiencies of the combination of Timmins, Balkan, and Tyler.

In view of the amendments and remarks presented above, Applicants submit that claims 30-31 are not unpatentable over any combination of Timmins, Balkan, Tyler, Venkatesh, and Bennett, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration of the application, withdrawal of the outstanding rejections, allowance of Claims 1-11, 13-26 and 28-31, and the prompt issuance of a Notice of Allowability.

Should the Examiner believe anything further is desirable in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account No. 01-2300, referencing attorney docket number 030363.00003.

Respectfully submitted,

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